Complete Summary

GUIDELINE TITLE

The diagnosis and management of urticaria: a practice parameter part I: acute urticaria/angioedema part II: chronic urticaria/angioedema.

BIBLIOGRAPHIC SOURCE(S)

The diagnosis and management of urticaria: a practice parameter part I: acute urticaria/angioedema part II: chronic urticaria/angioedema. Joint Task Force on Practice Parameters. Ann Allergy Asthma Immunol 2000 Dec;85(6 Pt 2):521-44. [139 references] PubMed

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Acute urticaria/angioedema
- Chronic urticaria/angioedema

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Allergy and Immunology
Dermatology
Family Practice
Internal Medicine
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To assist in the clinical decision making for diagnosis and management of acute and chronic urticaria/angioedema

TARGET POPULATION

Adults, adolescents, and children presenting with symptoms consistent with a diagnosis of urticaria (pruritic [and sometimes painful or burning], erythematous, circumscribed [or coalescent] wheals) and/or angioedema (subcutaneous swelling)

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation/Diagnosis

1. Detailed history including review of systems:
    - Drug exposures
    - Food exposures
    - Physical triggers
    - Infection exposures, especially viral hepatitis
    - Occupational exposures
    - Insect stings or bites
    - Physical sensitivity (e.g., cold stimulus)
2. Physical examination of skin, lymph nodes, eyes, joints, throat, neck, ears, lungs, heart, and abdomen in an effort to detect an associated underlying condition (e.g., connective tissue disorders, thyroid disease, lymphoreticular neoplasms)
3. Laboratory studies including complete blood count with differential; urinalysis; erythrocyte sedimentation rate; liver function tests
4. Specific diagnostic testing including:
    - Allergen skin testing
    - In vivo/in vitro assessment of specific immunoglobulin E (IgE)
    - Tests for Epstein Barr virus (e.g., Monospot™)
    - Complement studies to exclude hereditary or acquired C1 esterase inhibitor deficiency
    - Double blind challenge format to confirm drug-associated etiology
    - Skin biopsy
5. Referral to allergist/immunologist/dermatologist

Treatment/Management

1. Emergency treatment (if appropriate)
2. Treatment of underlying conditions
3. Patient education/counseling regarding avoidance/elimination of specific allergens, use of food diary, use of emergency epinephrine kit as needed
4. Medications:

- Antihistamine therapy (e.g., Cetirizine [Zyrtec], Loratadine [Claritin], Fexofenadine [Allegra], Hydroxyzine HCl [Atarax or Vistaril], Diphenhydramine [Benadryl], Doxepin [Sinequan])
- Tricyclic antidepressants as warranted
- Anti-inflammatory agents (e.g., short course oral glucocorticosteroids)
- Leukotriene modifiers (discussed but not recommended)

5. Follow up may include:
    - Prophylactic medication
    - Periodic urinalysis and creatine clearance
    - Referral to nephrologist and/or ophthalmologist

MAJOR OUTCOMES CONSIDERED

- Incidence of urticaria associated with angioedema
- Incidence of urticaria or angioedema occurring exclusively
- Incidence of associated or underlying conditions (e.g., infectious illness, gastrointestinal parasites, food or medication allergies, etc.)
- Symptom presentation
- Effectiveness of laboratory tests

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The initial drafts of the acute and chronic urticaria/angioedema sections were prepared by the guideline authors. Extensive discussions of these drafts by the Joint Task Force on Practice Parameters resulted in consensus about the major body of recommendations, all of which were referenced by appropriate publications in the literature.

Some of the material in the draft document could not be referenced in this fashion. When this situation arose, the Task Force reached consensus by considering the clinical experience of the Task Force as well as designated consultants.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Peer review of the revised draft was conducted by independent board certified experts selected by the governing bodies of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology. Appropriate suggestions for modification that could be documented by literature sources by these individuals were then incorporated into the final draft of the document. Consensus opinions for which evidence was ambivalent or controversial are italicized in the original guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

This practice parameter consists of two parts: (1) acute urticaria/angioedema and (2) chronic urticaria/angioedema. The recommendations in each part are presented in the form of an algorithm accompanied by annotations (numbered to correspond with the algorithm).

Part 1: Acute Urticaria/Angioedema Algorithm

Acute Urticaria/Angioedema Annotations

1. Patient presents with possible acute urticaria and/or angioedema

   Urticaria and/or angioedema are generally referred to as acute if they are of less than 6 weeks duration. Acute urticaria occurs more commonly in children and young adults, whereas chronic urticaria is more common in "middle-aged" women. It is useful to characterize urticaria as acute in a patient who is experiencing urticaria for the first time or who has had recurring acute urticarial events, versus the patient who has a history of urticaria for several weeks on a continuous basis. In the former group of patients, the etiology may be readily apparent to both the patient and the physician. For example, the etiology may be obvious in a patient who presents with acute urticaria after drug administration, an insect sting, or repetitively following exposures to cold. If the cause of an acute episode of hives is obvious to both patient and physician, a detailed history and physical are not required. (Proceed to Annotation 3) In contrast, the longer the urticaria has been continuously present, the more difficult the etiology is to determine.

   As many as 15% to 24% of the U.S. population will experience acute urticaria and/or angioedema at some time in their lives. Urticaria should be considered when the patient presents with pruritic (and sometimes painful or burning), erythematous, circumscribed (or coalescent) wheals. Urticarial lesions commonly involve the extremities and trunk but may appear on any part of the body. Angioedema manifests itself as deeper subcutaneous swelling. Less circumscribed than the lesions of urticaria, angioedema has a predilection for areas of loose connective tissue such as the face, eyelids or mucous membrane involving the lips, and tongue. If tissue distention involves sensory nerves, angioedema lesions may be painful or paresthetic. Location and/or duration of the lesions may provide clues to the etiology of the process. Thus, lesions due to cold exposure, exercise or dermatographism typically last less than 2 hours and lesions of urticarial vasculitis appear predominantly on lower extremities and persist without change in morphology for longer than 24 to 48 hours.

   Clinical presentations of urticaria/angioedema may encompass dermatographism [i.e., exaggerated triple response of Lewis (local reddening, edema and surrounding flare)], papular urticaria, localized urticaria, cutaneous and mucosal manifestations of anaphylaxis/anaphylactoid reactions or an underlying disease. Angioedema may occur with or without urticaria. In the latter circumstance, hereditary or acquired complement 1 (C1) esterase inhibitor deficiency should be suspected.

   Acute urticaria and/or angioedema may begin suddenly, with physical manifestations appearing over a period of minutes to hours, or may evolve insidiously over a longer period of time. The evanescent, transient time course of acute urticaria and/or angioedema lesions is characteristic of the process.

If angioedema involves the upper respiratory tract, life-threatening obstruction of the laryngeal airway may occur. Hereditary or acquired angioedema associated with C1 esterase deficiency are particularly prone to this presentation, although other forms of angioedema can present with glossopharyngeal edema causing hoarseness and difficulty in swallowing. Presentations such as this, however, accentuate the importance of evaluating the patient who presents with acute urticaria and/or angioedema for the need of emergency treatment, as urticaria and/or angioedema may be early signs in the evolution of anaphylaxis. A detailed history and physical examination may need to be deferred until emergency treatment has been administered.

2. Detailed History and Physical Examination

To maximize the possibility of discovering the specific etiology of acute urticaria and/or angioedema, a detailed history of the circumstances preceding and surrounding the onset of the condition is necessary. This should include, but not necessarily be limited to, the following information: (1) current or previous medications, herbals, or supplements (including excipients) which the patient has used and the time they were started in relationship to the appearance of the lesions; (2) relationship to food exposures (ingestion, inhalation, contact) and the onset of urticaria and/or angioedema; (3) relationship of potential physical triggers, e.g., cold, exercise, heat, sweating, pressure, sun (or light) exposure; (4) exposure to infectious processes, such as a respiratory virus, viral hepatitis, or infectious mononucleosis; (5) occupational exposure to allergens or irritants; (6) any recent insect sting or bite; (7) contact exposure due to high or low molecular weight allergens; (8) allergen exposure by inhalation; and (9) a complete review of systems to include systemic diseases, such as autoimmune, connective tissue and lymphoproliferative disorders.

A thorough physical examination should, at a minimum, include examination of the skin, lymph nodes, eyes, joints, throat, neck, ears, lungs, heart, and abdomen in an effort to detect an associated underlying condition (e.g., connective tissue disorders, thyroid disease, lymphoreticular neoplasms). (See Commentary 1 in original guideline document. See also the related guideline "Disease Management of Drug Hypersensitivity: A Practice Parameter" [Ann Allergy Asthma Immunol 1999;83:S665-S700].)

3. Is evaluation suggestive of an underlying cause?

Specific findings on physical examination or clues developed from the clinical history may direct the evaluation towards an identifiable trigger for the urticaria and/or angioedema. Pertinent infectious exposures, food ingested within several hours prior to the appearance of symptoms several hours after ingestion, medication use preceding the appearance of lesions, or occupational exposures may allow the diagnostic focus to be narrowed to a few suspect triggers. These clues are important given the plethora of potential urticarial triggers and the inherent difficulty in identifying triggers responsible for sporadic urticarial reactions (see Commentary 1 in original guideline document).

On examination, the presence of: thyroid enlargement (suggesting an autoimmune process and/or hormonal dysregulation); lymphadenopathy or visceromegaly (suggesting an underlying lymphoreticular neoplasm); or joint, renal, central nervous system, skin or serous surface abnormalities (suggesting a connective tissue disorder) will similarly focus the evaluation. The presence of dermatographism (urtication on stroking of the skin) suggests the presence of a physical urticarial process. Similarly, examination procedures directed to other suspected physical urticarias, (e.g., cold, heat or solar urticaria/angioedema) can be employed for diagnosis. Cold, heat, and light tests are available for these respective physical urticarias. Localized hives or edema at pressure sites also point to a physical trigger for the urticarial process. Pinpoint hives after exercise or heat exposure suggest a possible cholinergic process. Concomitant manifestations of a more general process (e.g., respiratory distress, hypotension, airway obstruction, gastrointestinal distress) accompanying urticaria should immediately redirect attention away from hives as the primary factor to an underlying anaphylactic process which necessitates rapid intervention.

Patients with acute urticaria and/or angioedema may represent a complex, multifactorial, evolving process. Evaluation, diagnosis, and management (both short-term and, if lesions persist beyond 6 weeks, long-term) may be challenging. For these reasons, patients presenting with acute urticaria and/or angioedema, for which the inciting triggers are not clear and easily avoided or initial therapy is not optimally effective, might be considered for referral to an appropriate specialist.

4. Specific evaluation

The specific evaluation of a patient presenting with acute urticaria and/or angioedema should focus on the findings suggested by the clinical history and physical examination. Patients with a specific food, drug or insect hypersensitivity should be evaluated with appropriate diagnostic tests. For instance, a patient presenting with acute urticaria in temporal relationship to a specific food, insect sting/bite or drug may warrant in vivo or in vitro assessment of specific immunoglobulin E (IgE) (if available) to that particular allergen in a controlled setting where the expertise and equipment needed to treat an anaphylactic reaction are available. If acute mononucleosis is suspected, appropriate tests for Epstein-Barr virus (e.g., Monospot™) could be confirmatory. The association of other infections with acute urticaria has not been sufficiently documented to recommend specific diagnostic tests. A patient presenting with recurrent episodes of acute angioedema of the face, tongue or lips, in association with bouts of severe abdominal discomfort without associated urticaria should be evaluated with specific complement studies to exclude hereditary or acquired C1 esterase inhibitor deficiency. Acute urticaria in association with the administration of penicillin or a related beta-lactam antibiotic may warrant diagnostic evaluation with penicillin skin testing. Allergen skin testing and/or in vitro tests for detection of specific IgE antibody to inhalants (e.g., animal danders, pollens, molds, etc) may be useful when the history reveals that urticaria/angioedema occurs after direct contact with a suspected allergen such as direct contact with animals, weeds, and grass. Physical findings of weight loss, lymphadenopathy, and

visceromegaly would warrant a further medical evaluation to exclude an underlying lymphoreticular malignancy.

5. Limited Evaluation/Treatment

In the absence of historic or physical examination findings leading to a suggested underlying cause, a limited laboratory diagnostic evaluation (including a complete blood count with differential, urinalysis, erythrocyte sedimentation rate, and liver function tests) may be considered, primarily to identify occult underlying conditions at a stage prior to a more overt clinical presentation. Concomitantly, or following such evaluation, interventional measures may be implemented. As previously stated, the immediate therapy of acute urticaria and/or angioedema as part of evolving anaphylaxis may necessarily take temporary precedence over diagnostic evaluation. Although there may be increased risks in elderly patients and patients with preexisting cardiovascular diseases, there are no contraindications to the use of epinephrine in acute life threatening situations. Removal of factors that may augment or induce urticaria/angioedema, (e.g., nonsteroidal anti inflammatory drugs [NSAIDs] or alcohol ingestion) may result in improvement and would thus seem appropriate in both acute and chronic presentations of urticaria/angioedema.

Since histamine is one of the primary mediators of urticaria, antihistamine therapy comprises the cornerstone of therapy for acute presentations of this condition. Continuous treatment with antihistamines over a period of weeks may suppress the urticarial process until a sustained remission occurs. With the advent of second-generation, low-sedating or non-sedating H1-antihistamines, the impact of treatment on mental alertness and quality of life can be minimized, primarily through the avoidance of the daytime sedation associated with the use of first-generation H1-antihistamines. Use of second-generation H1-antihistamines, (e.g., loratadine, fexofenadine, or cetirizine) may be quite effective in controlling the urticarial process without side effects although cetirizine may be mildly sedating in some patients (see Commentary 2 in original guideline document). When necessary to achieve optimal hive and pruritus control, as-needed doses of first-generation H1-antihistamines, (e.g., hydroxyzine or diphenhydramine) may be added to or given in place of these agents. Caution is warranted in carefully building up the dose of older, sedating antihistamines, especially in the treatment of patients involved in occupations that require the operation of machinery or vehicles, or where constant mental alertness cannot be compromised. To facilitate necessary medication regimen adjustments, an open line of communication between patient and physician is essential during this initial phase of therapy. If optimal doses of H1-antihistamines do not provide adequate hive control, H2-antihistamines, (e.g., ranitidine or cimetidine) may be added to the regime. Tricyclic antidepressants such as doxepin, possessing more potent H1 and H2-antihistamine properties than some first-generation classical antihistamines, may have a role in therapy, although side effects such as dry mouth may limit their tolerability.

The routine use of glucocorticosteroids in the treatment of patients with acute urticaria and/or angioedema is rarely necessary. When considered essential for acute management, short courses of oral glucocorticosteroids rather than

depot parenteral preparations are preferred, to lessen the duration of systemic effects.

There are preliminary reports about the potential usefulness of leukotriene modifiers in the treatment of chronic urticaria. Until such potential leukotriene-modifying approaches are evaluated in groups of acute urticaria patients, their clinical use remains empirical (although potentially justifiable for patients refractory to conventional therapies or in patients for whom avoidance of glucocorticosteroid therapy is desired).

6. Is additional evaluation suggestive of underlying etiology?

   In the proper clinical context, the finding(s) of specific, confirmatory laboratory data, [e.g., a positive in vitro assay for a food allergen; a low C4 level; abnormal functional/quantitative assays of C1-esterase inhibitor protein; a positive skin test for penicillin; or an abnormal hemogram confirmed by specific hematologic investigations (bone marrow examination, abdominal computed tomography scan, etc,) supporting the presence of an underlying lymphoreticular malignancy] may verify the initial diagnostic suspicions of particular specific etiologies for the urticarial process. If a cause has not been determined at this point, the associated chronicity and complexity of the underlying process and its clinical management may warrant referral to an appropriate specialist.

7. Manage specific condition

   When a specific etiology of the urticaria and/or angioedema has been identified, avoidance/elimination of the inciting trigger(s) assumes the central role (e.g., avoidance of specific food allergens, drugs, or trauma that induces angioedema in a patient with hereditary or acquired C1 esterase inhibitor deficiency). Although the etiology of acute urticaria and/or angioedema may be easier to discover than that of chronic urticaria and/or angioedema, the cause or causes may still elude identification. The patient should be counseled regarding this issue, emphasizing the benign prognosis of the condition, provided that history, physical examination, or laboratory features do not suggest a more serious underlying process.

8. Follow up, if symptoms persist

   The persistence of urticaria and/or angioedema beyond 6 weeks, despite appropriate acute evaluation and intervention necessitates a reorientation towards a chronic process, and may thus warrant further evaluation discussed in the accompanying algorithm on evaluation of chronic urticaria and/or angioedema (see Part 2). At this point, referral to an allergist/immunologist is appropriate, especially if the etiology has not been conclusively determined.

Part 2: Chronic Urticaria/Angioedema Algorithm

Chronic Urticaria/Angioedema Annotations

1. Does patient exhibit skin lesions consistent with chronic urticaria and/or angioedema?

   Urticaria is characterized by pruritic, erythematous, blanching, circumscribed macular or raised lesions involving the superficial layers of skin. Urticarial lesions classically wax and wane and do not persist in a given location for more than 24 hours. Such lesions are defined as chronic if manifestations are persistent or recurring over 6 weeks in duration (see Figure 1b in original guideline document). Persistent symptoms may be daily or episodic (weekly, monthly, etc). Diurnal patterns are often reported but these are highly variable from patient to patient. It is not possible to predict the duration of chronic urticaria/angioedema. Spontaneous remissions often occur within 12 months but a substantial number of patients continue to have symptoms at least periodically for years. Conditions that can masquerade as urticaria include but are not limited to the following entities: erythema multiforme minor, non-specific maculopapular exanthems, and mast cell releasability syndromes such as urticaria pigmentosa, (see Commentary 1 of Acute Urticaria and Commentary 1 of Chronic Urticaria in the original guideline document for details). Hypersensitivity vasculitis (i.e., urticarial vasculitis) should also be excluded (see Annotations 4 through 6). The skin lesions of urticarial vasculitis present with an urticarial appearance, but differ in that they persist 24 hours or longer in the same area, and may be palpable and purpuric. Following resolution, these lesions may leave residual pigmented changes in the skin. Urticarial vasculitis may be limited to the skin or be part of a systemic disorder. On occasion, patients with pruritus alone are referred for urticaria evaluation (see Commentary 1 in original guideline document for details). Angioedema involves swelling of deep subcutaneous regions in the skin and/or mucous membranes, such as a finger, hand, lip, tongue etc. There are many conditions that can masquerade as angioedema that must be considered when evaluating this skin manifestation (see Commentary 1 of Acute Urticaria and Commentary 1 of Chronic Urticaria in original guideline document for details).

2. Does the patient have chronic angioedema without urticaria?

   Commonly, patients experience the coexistence of chronic urticaria and angioedema. However, some patients may present with chronic angioedema without urticaria. Patients with this manifestation fall into a separate category that may require diagnostic evaluations for unusual conditions (see Annotation 3). The evaluation should move to Annotation 4 if there is urticaria with angioedema.

3. Evaluation of chronic angioedema without urticaria

   A detailed history, and physical examination are suggested to rule out underlying causes. Of particular importance is the family history because of the possibility of hereditary angioedema. Etiologic triggers include medications (e.g., angiotensin converting enzyme (ACE) inhibitors) occupational exposure (e.g., latex sensitivity); insect sting reactions; physical hypersensitivity disorders (e.g., cold urticaria that can present with generalized or regional angioedema following cold exposure); exercise-induced angioedema with or without anaphylaxis; pressure-mediated

sensitivity that can cause angioedema of the feet following walking or running and less often food hypersensitivity. The managing physician may require the expertise of an allergist/clinical immunologist to evaluate unusual causes of angioedema (see Annotation 8 for other etiologies).

A history of angioedema alone may suggest a rare disorder of C1 esterase inhibitor deficiency, which may be inherited as a autosomal dominant or acquired angioedema due to C1 esterase inhibitor deficiency may present as an acute episode of regional swelling following trauma (e.g., dental manipulation of the oropharynx) or episodic abdominal pain which is thought to be secondary to angioedema involving the intestinal tract. Although C1 esterase inhibitor deficiency may present as an acute episode, detailed history may confirm the recurrent nature of these disorders. It is advised that screening C4 levels be obtained on all patients with chronic angioedema without urticaria, especially patients with the aforementioned history. C4 levels are usually decreased during both symptomatic and asymptomatic periods of the disease, while C2 levels are reduced only during attacks. If the C4 level is reduced, quantitative C1 esterase inhibitor levels should be obtained. If these levels are normal, a functional assay should then be done. Fifteen percent (15%) of patients with hereditary C1 esterase inhibitor deficiency have evidence of dysfunctional inhibitor protein with normal quantitative levels of C1 esterase inhibitor.

Patients with chronic angioedema without urticaria may have acquired C1 esterase inhibitor deficiency associated with a lymphoproliferative disorder or a systemic connective tissue disease. A reduced C1q in association with decreased C1 esterase inhibitor and C4 warrants evaluation for an occult lymphoproliferative disorder. The presence of C1q autoantibody and/or C1 esterase inhibitor autoantibody suggests an underlying connective tissue disease although it may be present without evidence of an underlying disease. C1q autoantibody is sometimes associated with lupus erythematosus.

3a. Is evaluation of chronic angioedema without urticaria suggestive of an underlying cause?

Appropriate laboratory testing is advised for confirmation of a specific cause of angioedema without urticaria. For example, a history of recurring angioedema of the hands after exposure to latex gloves requires an in vitro blood test (i.e., enzyme-linked immunosorbent assay [ELISA], dot blot) and/or a carefully applied skin prick/puncture test with latex protein. Screening for the C4 complement component should be obtained for suspected C1 esterase inhibitor deficiency. An individual who experiences swelling of the lips after eating cold foods should have a localized (ice cube) cold stimulation test to diagnose cold-induced urticaria/angioedema. Other examples of laboratory confirmation are described in Commentary 3 in the original guideline document. On occasion, a suspected cause of angioedema without urticaria can only be established by history. Examples are angioedema caused by drugs such as angiotensin-converting enzyme (ACE) inhibitors or aspirin/NSAIDS. There are no reliable in vitro tests that can confirm a drug-associated etiology. If there is a crucial need for the drug, a more definitive relationship of cause and effect can be obtained by withdrawal

of the suspected drug followed by a double blind challenge format. This procedure should be performed by physicians with expertise in monitoring this test.

3b. Specific management of an underlying cause of chronic angioedema without urticaria

Individuals with recurrent angioedema that is a manifestation of anaphylaxis should carry an emergency epinephrine kit (e.g., Epipen). In addition, specific management should be instituted once an etiology of angioedema without urticaria has been established. Latex-induced angioedema would require elimination of latex exposure and possible removal of cross-reacting food allergens from the patient's diet (e.g., banana, avocado, grapes, peaches, apricots, cherry, pineapple, kiwi, chestnut, etc). Recurring urticaria/angioedema due to cold sensitivity requires avoidance of cold exposure, particularly immersion (e.g., aquatic activities) and possible prophylaxis with cyproheptadine, second generation antihistamines or doxepin.

The treatment choices for recurrent acute life threatening attacks of C1 esterase inhibitor deficiency (hereditary or acquired) are limited and usually supportive. Some clinicians advocate treatment with plasma infusions or C1 esterase inhibitor concentrates although the latter are not commercially available. Should these measures fail, intubation or tracheostomy may be necessary. For frequent episodes of angioedema due to C1 esterase deficiency, prophylactic management is possible with anabolic steroids (e.g., Danazol or Stanazolol®). Because of the danger of trauma-induced exacerbations, short-term prophylactic anabolic steroids 4 to 5 days prior to elective dental or surgical procedures should be considered. Annotations 10, 13, 14 discuss nonspecific considerations for treatment of angioedema with or without urticaria.

4. Do patients with chronic urticaria (with or without angioedema) exhibit lesions suggestive of urticarial vasculitis?

Although the prevalence of urticarial vasculitis is low, it is nevertheless important to recognize because this disease can be associated with other systemic conditions (i.e., the Henoch-Schönlein syndrome) and is amenable to effective treatment. If skin lesions have an urticarial appearance and last longer than 24 hours in the same location, urticarial vasculitis (i.e., hypersensitivity vasculitis) should be considered. Typically these urticarial-like lesions: (1) are less pruritic and more painful than observed with true chronic urticaria, (2) are more prominent on lower extremities, (3) may be palpable and purpuric, and (4) following resolution may leave pigmented changes in the skin. Angioedema may accompany urticarial vasculitis. In addition, urticarial vasculitis may be associated with systemic symptoms such as low-grade fever, arthralgia/arthritis, gastrointestinal complaints, pulmonary and ocular symptoms. Urticarial vasculitis is thought to be due to immune complex mediated inflammation (see Commentary 2 in the original guideline document for details on mechanism). The evaluation should move to Annotation 8 if urticarial lesions remain less than 24 hours in the same location.

Occasionally, history and examination may not provide definitive evidence of urticarial vasculitis. If urticarial vasculitis is suspected, it may be necessary to evaluate specific lesions at 24 hours, 36 hours, and 48 hours after the initial evaluation. Specific lesions should be circled and numbered as part of the ongoing assessment. Lesions that remain fixed beyond 24 hours require further diagnostic evaluation for urticarial vasculitis (see Annotation 5).

5. Evaluation of suspected urticarial vasculitis

If urticarial vasculitis is suspected, a punch biopsy of a suspected skin lesion should be obtained. Urticarial vasculitis lesions reveals a specific histopathology described in Annotation 6. Immunofluorescence of the skin biopsy may determine the presence of fibrinogen, immunoglobulin (e.g., IgA, IgG, and IgM) and/or complement deposition, several or all of which are indicative of immune complex mediated events. Other tests that may be useful include complement assays to rule out complement depletion (e.g., CH50, C3, Factor B, and C1q) and cryoglobulins. Immune complex assays (Raji assay and C1q binding) have limited sensitivity and specificity. The erythrocyte sedimentation rate and/or C-reactive protein may be elevated in urticarial vasculitis.

6. Does patient have urticarial vasculitis?

The diagnosis of urticarial vasculitis is confirmed by the histopathologic results of the skin biopsy. This includes polymorphonuclear infiltration within the walls of blood vessels and in the perivascular space. Leukocytoclasia (i.e., fragmentation of neutrophils) is frequently noted along with endothelial swelling, red blood cell extravasation and fibrin deposition. Complement levels (e.g., CH50) may be normal or decreased in this condition. Hypocomplementemia associated with urticarial vasculitis has a worse prognosis and is suggestive of systemic disease. A decreased C1q level may be a sensitive marker of complement activation in patients with urticarial vasculitis. If there are decreased complement indices and/or C1q levels, a more thorough evaluation for systemic disease involving the renal, gastrointestinal, pulmonary, ocular, and musculoskeletal systems should be considered. Other serious diseases should be considered in the differential diagnosis of vasculitis (see Commentary 2 in the original guideline document).

7. Management of urticarial vasculitis

Patients with urticarial vasculitis should be managed by physicians with expertise in these conditions. Antihistamines may be useful in managing the pruritus associated with urticarial vasculitis (see Annotation 14). Other symptoms due to immune complex-mediated inflammation may not respond to antihistamine therapy. Patients with moderate or severe cutaneous disease, especially those with systemic manifestations, may require treatment with anti-inflammatory agents, such as: glucocorticosteroids, indomethacin, colchicine, dapsone and hydroxychloroquine. Cytotoxic agents (e.g., methotrexate, azathioprine, cyclosphosphamide) can be used cautiously to reduce the dose requirements of corticosteroids. Patients receiving these

medications require careful monitoring for potentially serious side effects associated with use of these agents.

Patients with urticarial vasculitis should be monitored for evidence of systemic disease that might affect the renal, gastrointestinal, pulmonary, ocular, and musculoskeletal systems. For example, periodic urinalysis and creatinine clearance (if indicated) should be performed to rule out renal involvement. Referral to a nephrologist may be indicated if significant and progressive renal abnormalities are detected. Annual ophthalmological referrals may also be appropriate.

8. Evaluation of chronic urticaria (with or without angioedema) to include detailed history, review of systems, physical examination and basic laboratory tests

   It is unusual to find an exogenous cause for chronic urticaria/angioedema. Nevertheless, every effort should be made to determine the etiology of these symptoms, especially by periodically obtaining a detailed history. Despite frustrating statistics, that a cause can only be confirmed in 5% to 20% of patients, it is helpful to evaluate patients based on broad categories of mechanisms such as: IgE-dependent mechanisms (e.g., drug, food, insect venom, and latex exposure); and complement-mediated mechanisms (e.g., hereditary angioedema and serum sickness). The evaluation should include a detailed history of: (1) medications administered for several weeks before and during the onset of symptoms; and (2) symptoms temporally related to ingestion of food(s). At the time of evaluation, most patients will already have considered foods as a cause for their urticaria, either on their own or on the advice of a physician. In the vast majority of adult cases, attempts at identifying a food allergen are unsuccessful. Other factors for consideration include (1) physical hypersensitivity; (2) underlying infection; (3) an autoimmune etiology; (4) possible hormonal effects, especially when hives in women occur on a cyclic basis; (5) manifestations consistent with malignancy; (6) pertinent occupational exposure; (7) multiple/repetitive or late onset reactions to insect stings/bites; (8) direct contact of skin or oropharynx with foods, chemicals, animal saliva, and other substances; (9) familial pattern that might suggest hereditary syndromes; and (10) psychologic stresses that might aggravate skin manifestations (see Commentary 3 in original guideline document for more history details).

   A detailed review of systems is warranted to uncover symptoms that may suggest a systemic disease etiology for chronic urticaria/angioedema. Multi-system symptoms involving joints, gastrointestinal tract, pulmonary, renal or ocular systems could suggest a systemic disease associated with urticaria/angioedema (e.g., vasculitis, collagen vascular disease). A complete physical examination may provide unsuspected clues to the etiology of chronic urticaria/angioedema. The physical evaluation should include all systems to rule out serious underlying diseases (e.g., malignancies, mixed connective tissue diseases, chronic hepatitis, chronic infections, cutaneous or systemic mastocytosis, cryoglobulinemia, etc). Association with other skin lesions may be helpful in the differential diagnosis of chronic urticaria; thus, residual discoloration of fading urticaria especially on the legs suggests urticarial vasculitis. Concomitant bullous eruptions would suggest cutaneous

blistering conditions such as bullous pemphigoid or dermatitis herpetiformis. Reddish tan pigmented macules that urticate on stroking would suggest urticaria pigmentosa. Palpable purpura on lower extremities is seen with cryoglobulinemias or leukocytoclastic vasculitis. Specific physical findings in the skin or other systems may direct the diagnostic evaluation.

Laboratory test confirmation is essential if an etiology is suspected by history and/or physical examination. If they have not already been obtained, basic laboratory tests are advised as a screening approach for underlying diseases. The panel might include a complete blood count, erythrocyte sedimentation rate, urinalysis and liver function tests. Because thyroid autoantibodies (anti-thyroglobulin and anti-thyroid peroxidase) and anti-Fc_e1 receptor antibodies are being reported with increasing frequency, some clinicians recommend that these tests be obtained if the initial screening panel is noncontributory and the urticaria/angioedema persists. Other tests could be added to the screening panel based on clinical indications. Specific laboratory tests should be selective and based only on diagnostic suspicions (see Commentary 3 in original guideline document for more testing details). If, at the initial presentation, chronicity of the patient's symptoms is already established in terms of months or years, it is justified to proceed directly to the next level of evaluation described in Algorithm Box 11 and Annotation 11. Under these conditions, evaluation of possible autoantibodies (e.g., thyroid, anti-high affinity, Fc_e1 receptor), as described above, and/or histopathologic data could be useful adjuncts in deciding optimal management (see Algorithm Box 10 and Annotation 10). Commentary 3 also provides additional information about other possible helpful diagnostic pathways to detect triggers of mast cell activation at this stage of the patient's evaluation.

9. Is the evaluation of chronic urticaria (with or without angioedema) indicative of an underlying cause?

An underlying cause may be determined after data have been accumulated and are consistent with the history, physical examination and laboratory tests. Refer to Commentary 3 for other causal relationships suggested by history, physical examination and confirmatory laboratory tests.

10. Specific management of chronic urticaria (with or without angioedema)

The management of urticaria/angioedema will, in part, be dictated by the etiology. For example, avoidance of offending antigens when identified (e.g., drugs, foods, venom from insect stings, latex, etc.) applies to generalized and localized contact urticaria caused by antigen-induced IgE mechanisms. Non-specific agents that are known to exacerbate urticaria/angioedema (aspirin, NSAIDS, opiates, alcohol); physical stimuli that cause symptoms such as cold, heat, deep pressure, exercise, solar radiation, etc. should be avoided. Several physical hypersensitivity syndromes respond to specific therapeutic regimens. Idiopathic (i.e., primary) acquired cold urticaria responds to prophylactic treatment with a variety of first generation antihistamines (in particular, cyproheptadine and hydroxyine), second generation antihistamines (loratadine, fexofenadine, and cetirizine) and tricyclic antidepressants (doxepin). Cholinergic urticaria can be treated with various antihistamines.

Delayed pressure urticaria is treated with first and second generation antihistamines and may require courses of oral glucocorticosteroids (e.g., daily or if possible, every other day treatment) or other regimens including dapsone, NSAIDS, and sulfasalazine. Selected cases of exercise-induced urticaria with or without anaphylaxis may require prophylactic treatment with first and/or second generation antihistamines which may help to reduce the frequency and/or intensity of attacks. A prescription for an emergency epinephrine kit (e.g., Epipen) is advised for individuals with a concomitant history of anaphylaxis or laryngeal angioedema. In addition, occult food or drug allergies in combination with exercise may induce symptoms. In such cases, it is advised that patients avoid food or drug ingestion several hours before and after exercise. Dermatographism is best managed by patient awareness not only concerning the relationship of hives to scratching but also the need for prophylactic treatment with antihistamines. It may be necessary to treat a suspected infectious disease associated with urticaria and/or angioedema, such as hepatitis C, with alpha interferon and/or ribavirin. Treatment of an autoimmune disorder associated with urticaria/angioedema is dictated by the specific autoimmune disease. For example, treatment of autoimmune thyroid disorders with thyroid hormone may be associated with improvement or remission of urticaria. Therapy of urticaria/angioedema occurring with other generalized diseases is dictated by the specific underlying condition (e.g., neoplasms, systemic vasculitis, collagen vascular disorders, etc.).

In addition to specific treatment of an underlying condition, management should be oriented towards palliation of symptoms. In general, removal of potential urticarial aggravants such as aspirin, NSAIDS, or alcohol is advised regardless of the underlying etiology. For most patients, symptomatic treatment with H1 antihistamines remains the mainstay of management. Sedation from first generation antihistamines may be desirable for reducing the discomfort of pruritus associated with urticaria. First generation antihistamines, however, may cause undesirable and potentially dangerous side effects including driving impairment and risk for fatal automobile accidents decreased workplace productivity, increased risk for occupational accidents, increased risk for falls in nursing home patients, and in children, impaired learning and academic performance. Importantly, studies have demonstrated that many patients may not perceive performance impairment from first generation antihistamines, and that there is no correlation between subjective perception of sedation and objective performance impairment. In contrast, second generation antihistamines (loratadine, fexofenadine, and cetirizine) at recommended doses are associated with minimal risk for these adverse effects, although cetirizine may have mild sedative effects. Accordingly, the decision to choose between first and second generation antihistamines for treatment of urticaria should consider these differences.

Both first and second generation antihistamines also exhibit anti-allergic and anti-inflammatory effects but such properties do not consistently contribute to the overall clinical responses induced by this class of drugs. Combinations of various antihistamines and alternative therapeutic regimens such as glucocorticosteroids, other anti-inflammatory agents, $beta_2$-agonists, calcium channel blockers and anti-leukotriene drugs are discussed in Annotation 14.

11. Further evaluation of chronic urticaria (with or without angioedema)

A more detailed review of the history, review of systems, and physical examination may be warranted to uncover a previously unrecognized underlying condition associated with urticaria/angioedema. The discovery process may in part require the physician's careful observation of the urticaria/angioedema process over a protracted period of time. New observations may emerge that can provide clues to an underlying diagnosis. Teaching the patient to become more observant may be helpful and has been widely recommended. For example, prolonged use of detailed diaries has been used in an attempt to identify triggers and give a sense of participation in care. This process rarely detects a cause and may lead the patient to develop an unhealthy obsession with his/her urticaria. On the other hand, patient participation can be accomplished by reinforcing the patient's adherence to treatment recommendation in the hope that the hives will spontaneously resolve. The long-term management of refractory chronic urticaria/angioedema is greatly facilitated when there is good rapport between physician and patient because continuous reassurance is required.

New observations may dictate more detailed review of systems, physical examination and specialized laboratory evaluation. For example, a patient may develop symptoms of hypothyroidism in association with chronic urticaria. A careful examination of the thyroid would then be advised along with tests to evaluate thyroid function and presence of autoimmune thyroid disorders (i.e., anti-thyroid peroxidase/anti-thyroglobulin antibodies and autoimmune panels). Since one or both thyroid autoantibodies may be present in up to 28% of patients with chronic urticaria/angioedema, some clinicians advocate that these tests be obtained, especially in women or in those patients with a family history of thyroid or other autoimmune disease. In other situations, the managing physician might consider other tests depending on assessment of new or additional information. For example, hematologic leukemic markers might be ordered in a patient with acquired cold urticaria with cryoglobulinemia in order to rule out an underlying chronic lymphocytic leukemia process. Imaging procedures may be helpful at this juncture, depending on the need to evaluate a specific anatomical region in more detail. As part of the on-going re-evaluation, repeat or more detailed multi-system screening blood test panels may be indicated.

Other areas of evaluation may include trial elimination diets initially and/or limited food specific IgE tests (i.e., percutaneous skin tests; in vitro tests) if foods are implicated by history or diary data as potential causes of the symptoms. In this situation, prick/puncture tests are preferable, provided dermatographism is not present. Positive food specific IgE tests would in turn suggest further confirmatory food elimination trials. Open-single or double-blinded placebo-controlled food, food additive, or drug challenges may also be useful. These challenge procedures require close monitoring for symptoms of anaphylaxis.

A skin test with autologous serum may reveal a wheal and erythema response suggesting the presence of anti-IgE or anti high affinity IgE receptor antibodies.

A body of clinical evidence is emerging that recommends a punch skin biopsy be performed on patients with difficult to treat chronic idiopathic urticaria. Two groups of chronic urticaria have been defined by skin biopsy results: (1) perivascular lymphocyte-predominant urticaria and (2) perivascular polymorphonuclear--predominant urticaria (i.e., neutrophils, scattered eosinophils and mononuclear cells). Several interesting clinical observations have been associated with each group. Patients with lymphocyte-predominant infiltrates are more responsive to antihistamine therapy. Patients with polymorphonuclear cell-predominant infiltrates are relatively resistant to antihistamines and will more likely require oral glucocorticosteroid treatment. In addition, patients having IgG anti-IgE or IgE receptor autoantibodies often exhibit evidence of perivascular polymorphonuclear cell-predominant infiltrates in skin biopsies. Eosinophil activation may occur later or be more persistent in patients without autoantibodies. The skin biopsy may also detect unsuspected urticarial vasculitis or mastocytosis. The latter requires metachromatic stains such as Giemsa or toluidine blue for detection of increased numbers of mast cells (usually >4 per high power field).

12. Is additional evaluation of chronic urticaria (with or without angioedema) indicative of an etiology?

    An underlying cause may be determined after data has been accumulated and analyzed from the history, physical examination, and laboratory tests. For example a skin biopsy might reveal unsuspected urticaria pigmentosa with evidence of mast cell aggregates revealed by metachromatic stains. Other examples might be evidence of symptom induction during open-single or double-blinded placebo-controlled food, food additive or drug challenges. At this juncture, the managing physician decides whether an underlying etiology has been established. Refer to Commentary 3 in original guideline document for other causal relationships suggested by history, physical examination and confirmatory laboratory tests.

13. Management of specific etiology of chronic urticaria (with or without angioedema)

    The management of urticaria/angioedema will, in part, be dictated by the specific etiology. For example, if a skin biopsy reveals either urticaria pigmentosa or mastocytosis, treatment would be tailored to this diagnosis and should include avoidance of trigger factors (e.g., friction) and non-specific mast cell releasing agents (e.g., alcohol, aspirin, opiates etc). Specific pharmacologic therapy might include combinations of antihistamines, cautious use of cycloxygenase inhibitors, photochemotherapy with oral 8-methylpsoralen (i.e., plus ultraviolet A [PUVA]), and/or oral disodium cromoglycate for bullous mastocytosis and gastrointestinal manifestations of systemic mastocytosis. Another example would be identification of a food as a possible cause demonstrated by an open single-blinded food challenge or a double-blinded placebo-controlled challenge. The managing physician would eliminate the putative food from the patient's diet. It is important to recognize that isolation of a food substance as a cause of chronic urticaria/angioedema is rare. Refer to Annotation 10 for more examples of specific management strategies dictated by diagnosis of an underlying disorder.

In addition to specific treatment of an underlying condition, management should be oriented towards palliation of symptoms which is also described in Annotation 10. For most patients, symptomatic treatment with antihistamines is advised and described in Annotation 10. If indicated, the use of glucocorticosteroids and other anti-inflammatory agents is outlined in Annotation 14.

14. Treatment of chronic idiopathic urticaria (with or without angioedema)

At this stage of the evaluation it is reasonable to define chronic urticaria/angioedema as idiopathic since this is a diagnosis by exclusion of underlying etiologies. If treatment is ineffective up to this point, referral to an allergist/clinical immunologist or dermatologist might be considered. The therapeutic management should first be oriented towards palliation of symptoms which is discussed in Annotation 10.

Combinations of various antihistamines may be useful in suppressing symptomatology. These include (1) first generation H1 antihistamines, (2) combinations of first and second generations using non-sedating agents in the morning and first generation drugs at night, (3) combinations of second generation antihistamines, (4) combination of an agent with both H1 and H2 anti-receptor activity (i.e., doxepin) with a first or second generation antihistamine, and (5) combination of an H2 anti-receptor antihistamine [e.g., cimetidine (Tagamet) or ranitidine (Zantac)] with a first or second generation antihistamine. Managing physicians should acquaint themselves with the side effects, as discussed in Annotation 10, and drug-drug interactions when using any combination of pharmacological agents.

Antihistamines may not be entirely effective in controlling urticaria because other capillary permeability inducing mediators are released (e.g., leukotrienes; prostaglandin D2; kinins; platelet activating factor, etc). Glucocorticosteroid treatment may be appropriate when antihistamines are not effective. These agents are helpful in controlling the inflammatory cell influx that can potentiate the urticaria by secondary release of histamine releasing factors and cytokines. Managing physicians should explain the potential side effects associated with glucocorticosteroids. In some clinical situations, the managing physician or patient may request more evidence to justify the initiation of glucocorticosteroid therapy. A skin biopsy with perivascular predominant-polymorphonuclear cell urticaria may justify initiation and continuation of glucocorticosteroid treatment. As soon as possible, glucocorticosteroid therapy should be discontinued or reduced to minimal requirements such as an every other day regimen to reduce potential side effects. On rare occasions, chronic urticaria/angioedema may not respond to prednisone. Empirically, some of these patients may respond to methylprednisolone (e.g., Medrol).

Alternative management and therapeutic regimens may be necessary in refractory forms of chronic urticaria/angioedema. Mast cell degranulation inhibitors [i.e., an oral beta-adrenergic agonist such as terbutaline or albuterol; an H1 antihistamine such as ketotifen (not available in the US);] may have a role in treatment of refractory conditions. Nifedipine, a calcium

channel blocker may be of some benefit in controlling symptoms, either alone or in combination with antihistamines. Preliminary reports suggest that anti-leukotrienes may be effective in treating some patients with chronic idiopathic urticaria. There are anecdotal reports that oral cyclosporine, colchicine, or dapsone may be helpful in selected cases of severe refractory chronic urticaria/angioedema. Repeated plasmapheresis over a 2-month period may be effective in controlling refractory chronic urticaria especially in patients with circulating IgG autoantibody to IgE or the high affinity IgE receptor. A recent report described the efficacy of intravenous immunoglobulin therapy in patients with severe chronic urticaria caused by circulating autoantibodies.

Glossopharyngeal and laryngeal angioedema deserve special attention as they may become life threatening or present as manifestations of anaphylaxis. Patients may present with other symptoms of anaphylaxis that may require emergency treatment, as discussed in Annotation 5 of Acute Urticaria. The mainstay of treatment for this emergency is epinephrine in doses dependent on the patient's age. Intramuscular administration of epinephrine in children has been shown to produce a faster time of action than subcutaneous administration. Other treatment modalities include parenteral H1 and/or H2 antihistamine antagonists and parenteral glucocorticosteroids. Close monitoring of vital signs and oxygen measurements (e.g., pulse oximetry; arterial blood gases) may be necessary, as rarely a patient (e.g., hereditary or acquired C1 esterase inhibitor deficiency) may require intubation to overcome a compromised airway.

CLINICAL ALGORITHM(S)

Clinical algorithms are provided for:

- Acute urticaria/angioedema
- Chronic urticaria/angioedema

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The original guideline document supplies references within the narrative to support the algorithm annotations. Supplemental information in the form of commentaries and a list of references is also provided.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Effective diagnosis, treatment and management of acute and chronic urticaria/angioedema

POTENTIAL HARMS

- The use of epinephrine may pose increased risks in elderly patients and patients with preexisting cardiovascular diseases.
- Cetirizine may be mildly sedating in some patients.
- Patients receiving anti-inflammatory agents require careful monitoring for potentially serious side effects.
- First generation antihistamines may cause undesirable and potentially dangerous side effects including driving impairment and risk for fatal automobile accidents decreased workplace productivity, increased risk for occupational accidents, increased risk for falls in nursing home patients, and in children, impaired learning and academic performance. Importantly, studies have demonstrated that many patients may not perceive performance impairment from first generation antihistamines, and that there is no correlation between subjective perception of sedation and objective performance impairment.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

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The diagnosis and management of urticaria: a practice parameter part I: acute urticaria/angioedema part II: chronic urticaria/angioedema. Joint Task Force on Practice Parameters. Ann Allergy Asthma Immunol 2000 Dec;85(6 Pt 2):521-44. [139 references] PubMed

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GUIDELINE DEVELOPER(S)

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GUIDELINE DEVELOPER COMMENT

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None available

PATIENT RESOURCES

None available

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